MARKED-UP VERSION OF AMENDMENTS

IN THE CLAIMS:

Claims 20 and 25-26 have been amended as follows (deleted portion stricken out and added portions in bold):

20. (Twice Amended) A fusion protein comprising (i) an antigenic protein isolated from Mycoplasma gallisepticum causing an antibody-antigen reaction with Mycoplasma gallisepticum immune serum or Mycoplasma gallisepticum infected serum and (ii) a signal polypeptide of Herpesvirus outer membrane protein, said signal polypeptide being ligated with said antigenic protein isolated from Mycoplasma gallisepticum at the N terminus thereof, **thereby to secrete said antigenic protein extracellularly.**

25. (Three Times Amended) A recombinant Avipox virus ~~in which~~ **having** a DNA coding for ~~the fusion protein according to claim 20 has been inserted, said DNA~~ **a fusion protein** comprising ~~a first DNA sequence~~ **(i) an antigenic protein** isolated from Mycoplasma gallisepticum and ~~coding for the antigenic protein of claim 20~~ **causing an antibody-antigen reaction with Mycoplasma gallisepticum immune serum or Mycoplasma gallisepticum infected serum**, and ~~a second DNA sequence isolated from a Marek's disease virus gene coding for outer membrane protein gB, said second DNA sequence coding for the signal polypeptide of claim 20~~ **(ii) a signal polypeptide of Herpesvirus outer membrane, said signal polypeptide being ligated with said antigenic protein isolated from Mycoplasma gallisepticum at N terminus thereof, thereby to secrete said antigenic protein extracellularly**.

26. (Three Times Amended) A recombinant live vaccine for anti-fowl Mycoplasma gallisepticum infection comprising as an effective ingredient a recombinant Avipox virus ~~in which~~ **having** a DNA coding for ~~the fusion protein according to claim 20 has been inserted, said DNA~~ **a fusion protein** comprising ~~a first DNA sequence~~ **(i) an antigenic protein** isolated from Mycoplasma gallisepticum and ~~coding for the antigenic protein of claim 20~~ **causing an antibody-antigen reaction with Mycoplasma gallisepticum immune serum or Mycoplasma gallisepticum infected serum**, and ~~a second DNA sequence isolated from a Marek's disease virus gene coding for outer membrane protein gB, said second DNA sequence coding for the signal polypeptide of claim 20~~ **(ii) a signal polypeptide of Herpesvirus outer membrane, said signal polypeptide being ligated with said antigenic protein isolated from Mycoplasma gallisepticum at N terminus thereof, thereby to secrete said antigenic protein extracellularly**, wherein the fusion protein is capable, upon administration into a host cell, of immunizing that cell against subsequent infection with Mycoplasma gallisepticum.

New claims 27-46 have been added.

REMARKS

By the present amendment, claims 20 and 25-26 have been amended and new claims 27-46 have been added.

Support for the amendments to claim 20 is found in particular on page 8, lines 14-16, and Examples 1-6.

Support for the amendments to claims 25-26 is found in particular in claim 20 as well as on page 8, lines 14-16 and Examples 1-6.

Support for new claims 27-28 is found in particular on page 10, lines 13-25.

Support for new claims 29-30 is found in particular on page 26, 8 last lines.

Support for new claims 31-33 is found in particular in claims 20 and 25-26 and on page 10, lines 2-12.

New claims 34-38 correspond to claims 22-24 and 27-28, respectively, but depend on claim 31.

New claims 39-40 correspond to claims 37-38, respectively, but depend on claim 32.

New claim 41 corresponds to claims 29-30 but depends on claim 32.

Support for new claims 42-44 is found in particular on page 8, lines 10-16.

Support for new claims 45-46 is found in particular on page 10, lines 13-25.

Claims 20-47 are pending in the present application. Claims 20-24 and 27-30 are directed to a fusion protein, claims 25, 32 and 39-44 are directed to a recombinant Avipox virus, claims 31 and 34-38 are directed to a DNA, and claims 26 and 45-46 are directed to a recombinant live vaccine.

As a preliminary, the Applicants wish to explain that the key teaching of the present invention does not lie so much in the use of a specific antigenic gene or specific signal polypeptide, but in the combination use of the DNA coding for Mycoplasma gallisepticum antigenic gene with the DNA coding for a signal polypeptide of Herpesvirus outer membrane. This combination enables the secretion of the antigenic protein from the host cells, and as a result, the highly effective vaccination against Mycoplasma gallisepticum.

This characteristic is quite in contrast to Saito and Yoshida, as clearly illustrated in the explanatory drawings, Exhibits A and B, attached to this response.

Specifically, Saito and Yoshida describe the production of an antigenic protein with both a signal sequence and a membrane anchoring sequence. These prior arts use the membrane anchoring sequence ligated with the DNA coding for the antigenic protein. The difference between the present invention and these prior art is illustrated and exemplified schematically on Exhibit A. As a result, even after the antigenic protein is expressed in the host cells, the antigenic protein remains anchored on the host cells due to the membrane anchoring sequence, and cannot be released from the host cells. Therefore, the antigenic protein cannot be secreted extracellularly from the host cells. This difference between the present invention and these prior arts is illustrated and exemplified on Exhibit B.

In contrast, the present invention uses the combination of the DNA coding for the antigenic protein of Mg with the DNA coding for the signal polypeptide of Herpesvirus outer membrane, instead of the membrane anchoring ligated with the DNA coding for the antigenic protein of Mg (as illustrated in Exhibit A). As a result, after the antigenic protein is expressed in the host cells, the antigenic protein can be released and secreted from the host cells due to the signal polypeptide instead

of the membrane anchoring sequence ligated with the DNA coding for the antigenic protein (as illustrated on Exhibit B).

In particular, Examples 1 and 3 in the present specification describe the actual construction of the recombinant fowl pox viruses (FPV) 40K-C and 40K-S having the DNA coding for Mg antigenic protein with the DNA coding for a signal polypeptide of Herpesvirus outer membrane, so as to secrete the antigenic protein extracellularly, Example 5 demonstrates that the recombinant viruses 40K-C and 40K-S induce antibodies against Mg highly efficiently, and Example 6 demonstrates that 40K-C and 40K-S will result in highly effective vaccination.

A person of the art would immediately understand that the characteristic of the present invention does not reside in the use of specific Mg antigenic protein or specific signal polypeptide, but resides entirely in the combination of the DNA coding for Mg antigenic protein with the DNA coding for a signal polypeptide of Herpesvirus outer membrane, so as to secrete the antigenic protein extracellularly. In other words, the teachings, illustrations and exemplifications of the present invention makes clear to a person of the art that substantially any Mg antigenic protein and any signal polypeptide of Herpesvirus outer membrane can be used other than those specifically exemplified in the present application.

The rejections set forth in the Office Action will now be discussed as follows.

INDEFINITENESS REJECTION

In section 10 of the Office Action, claims 25-26 are rejected under 35 U.S.C. 112, second paragraph, as indefinite. It is alleged in the Office Action that claims 25-26 "recite a first and second

DNA sequence of claim 20" and that such DNA sequences lack a definition and thus antecedent basis in claim 20.

The rejection is respectfully traversed. It is submitted that claims 25-26 do not recite "a first and second DNA sequence of claim 20" as alleged in the Office Action, but "a DNA coding for the fusion protein according to claim 20," "a first DNA sequence... coding for the antigenic protein of claim 20," and "a second DNA sequence... coding for the signal polypeptide of claim 20." Thus the reference to claim 20 concerns the fusion protein, the antigenic protein, and the signal polypeptide, respectively. These terms are properly and clearly defined in claim 20, so that appropriate antecedent basis for each of these terms is provided for these features of claims 25-26.

Further, in claims 25-26, the first DNA sequence is defined as (i) isolated from Mg, and (ii) coding for the antigenic protein of claim 20, while the second DNA sequence is defined as (i) isolated from MDV gene coding for outer membrane protein gB, and (ii) coding for the signal polypeptide of claim 20. Accordingly, it is submitted that the DNA sequences have been clearly and sufficiently defined, so that claims 25-26 are not indefinite.

However, with a view at reducing the number of issues in the present application, claims 25 and 26 have been amended to delete the references to claim 20 but defining the antigenic protein and signal polypeptide as in claim 20.

In addition, new claims 31-33 recite a first DNA segment and a second DNA segment without referring to claim 20. It is submitted that claims 31-33 are also clear and definite.

In view of the above, it is submitted that the indefiniteness rejection should be withdrawn.

LACK OF WRITTEN DESCRIPTION REJECTION

Next, in section 8 of the Office Action, claims 25-26 are newly rejected under 35 U.S.C. 112, first paragraph, for lack of written description. It is alleged in the Office Action that (i) "[t]he written description of antigenic proteins and signal polypeptides not described by their DNA sequences is not commensurate in scope with the claims" (page 8, second full paragraph), (ii) neither the claims nor the specification teach the first and second sequences "when claim 20 does not teach any sequences" (Id.), and it is referred to the Federal Circuit decisions in Vas-Cath Inc. v. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991), Fiers v. Sugano, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993), Amgen v. Chugai, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991), and Eli Lilly, for the proposition that the sequence of the nucleic acid itself is required, while the recitation of a functional activity alone is insufficient (page 9, first and second full paragraphs).

Reconsideration and withdrawal of the rejection is respectfully requested. It is submitted that, in the present application, the DNA and protein sequences are not defined only by their functional activity, but also by their origin, in particular the origin from which they are isolated, so that a sufficient description of the DNA and protein sequences has been provided in the application to show that the inventors were in possession of the invention.

Thus, the present case does not concern the discovery of a gene per se, as in Amgen, Fiers, and Eli Lilly, but to the discovery of a hybrid DNA construct and corresponding fusion protein. Thus, the present invention can be practiced by a person of the art without the recitation of a specific sequence in the claims, as such sequences can be easily selected by the person of ordinary skill in the art.

More particularly, to complete the case law cited in the Office Action, reference is made to the Federal Circuit decision in Enzo Biochem Inc. v. Gen-Probe, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002), which clarifies that Eli Lilly did not institute a requirement for amino acid sequencing per se. Specifically, in Enzo, the DNA sequences were defined in the claims by their hybridization properties in relation to a list of deposited cells, while three exemplary sequences were deposited with ATCC. The court vacated the district court summary judgement of invalidity for lack of written description. The court refused in particular to subscribe to the district court's position that Eli Lilly always mandates the recitation of a sequence to comply with the written description requirement.

Similarly to Enzo, here, the present claims define the origin of the DNA/protein sequences, and the specification provides, like the exemplary sequences in a depository of Enzo, exemplary DNA sequences corresponding to the sequences defined in the present claims. Further, it is submitted that a person of the art would immediately understand that the recited DNA and protein sequences can be obtained from the recited origin by conventional methods in the art, when the teachings of the present specification are followed. Thus, it is submitted that the indications and illustrations in the present application make clear to a person of the art that the inventors were in possession of the invention for the full claimed scope. Accordingly, it is submitted that the present claims meet the written description requirement.

Reference is also made to the Written Description Guidelines, MPEP 2163 (page 2100-156, right col.) which suggest complying with the written description requirement by disclosing "a known or disclosed correlation between that function and the structure of the sequence." Here, again, the present invention does not focus on a newly discovered gene but is based on a hybrid DNA construct

and corresponding fusion gene. The present inventors have fully described the origin of the sequences and the construction of the hybrid DNA and fusion protein, and therefore, they have provided a sufficient description of the invention.

In particular, it is submitted that the present specification describes in details, for example, from page 8, lines 11 to page 8, line 3, various types of antigenic proteins and genes coding therefor. It is submitted that genes coding for the antigenic proteins are well known per se as illustrated for example in U.S. Patents No. 5,621,076, No. 5,766,594 and No. 6,322,780.

Further, the present specification also describes in details, for example, from page 8, line 4 to page 9, line 14, various types of the signal polypeptide derived from Herpesvirus outer membrane protein as well as the construction of the signal polypeptides. Thus, a person of the art could easily apply this teaching to various signal polypeptides, as illustrated by the articles Eur. J. Biochem., 213, 3, 1333-1340 (1993) (describes a construction method of the signal polypeptides based on hydrophobic regions) and Cell Immunol., 69, 2, 226-237 (1996) (describes a signal polypeptide of interleukin), excerpts of which are attached to this response.

In summary, present claims 25-26 are clearly sufficiently described in the present application.

In addition, regarding new claims 31-33, these claims clearly recite that the origin from which the first and second DNA fragments are isolated. Thus, a person of the art would immediately and clearly understand which sequences are encompassed by the present invention.

Further, with respect to claims 21 and 27-28, these claims recite specific sequences, respectively, for antigenic protein (claim 21), signal polypeptide (claim 27), and both antigenic protein and signal polypeptide (claim 28). The same remark is valid for claims 37 and 39 which recite

corresponding DNA signal sequence, and for claims 38, 40 and 45-46 which recite the full sequence for the DNA encoding the fusion protein. Accordingly, these claims are clearly described in the present application.

In view of the above, it is submitted that the lack of written description rejection should be withdrawn.

LACK OF ENABLEMENT REJECTION

Next, in section 4 of the Office Action, claim 26 remains rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. It is alleged in the Office Action that Example 6 in the specification is limited to 40K-S and 40K-C vaccines, so that undue experimentation would be required to determine the effectiveness of the generically defined vaccines in claim 26 because "the vaccine art is highly unpredictable."

Reconsideration and withdrawal of the rejection is respectfully requested. It is submitted that the person of ordinary skill in the art would immediately understand that the mechanism of the present invention does not rely in a particular antigenic gene, but in the combination of the antigenic gene and the signal sequence to result in secretion from the host cells, as discussed above in the introductory remarks. Thus, that person would immediately understand that the superior vaccine effects, as compared to the antigenic gene alone, is not due to the specific antigen gene or the specific signal sequence but to the combination as recited in the present claims.

In other words, based on the disclosure of the present specification and the exemplary illustration of the vaccine effects of 40K-S and 40K-C vaccines, and using the common knowledge in the art, as discussed in the previous section, a person of ordinary skill in the art would know how

to prepare the recombinant live vaccine of claim 26 with reasonable expectation of success. Therefore, present claim 26 is enabled.

In addition, with respect to claims 45-46, these claims recite the specific SEQ ID NOs. corresponding to the examples reported in the specification. Thus, these claims are clearly enabled.

In view of the above, it is submitted that the lack of enablement rejection should be withdrawn.

PRIOR ART REJECTIONS

Finally, in sections 6-7 of the Office Action, claims 20-24 remain rejected under 35 U.S.C. 103(a) as obvious over WO 94/23019 to Sajto (Sajto) [reference being made to the English version in US 5,871,742 to Saitoh et al.], in view of Yoshida et al., Virology 200, 484-493 (1994) (Yoshida), and claims 25-26 remain rejected under 35 U.S.C. 103(a) as obvious over Sajto in view of Yoshida and further in view of Yangida.

It is alleged in the Office Action that the discussion of the deficiencies of Sajto in vivo is not convincing because "antibody-antigen response is not limited to in vivo responses" and antigenicity in vivo is not recited in the claims.

Reconsideration and withdrawal of the rejection is respectfully requested.

It is submitted that the deficient results in vivo shown by Sajto are the reason why a person of ordinary skill in the art would not use the disclosure in Sajto to prepare hybrid DNA, fusion proteins, recombinant viruses with a view at preparing a live vaccine. Thus, a person of ordinary skill in the art would never be motivated to use Sajto alone or in combination with another reference such as Yoshida to arrive at the present invention, because the disappointing results of Sajto in vivo would

negate any motivation provided by its in vitro results. In other words, the disclosure of Sajto is completely insufficient to provide a motivation to use its teachings, whether or not in vivo results are recited in the claims.

In addition, even though Yoshida discloses that FPV recombinant expresses the gB-1 gene, and indicates accordingly that FPV recombinant is a good candidate for a MDV vaccine and gB is an important target for the host immune response, the teaching in Yoshida is limited to the insertion of the full length of gB, including its signal sequence and its membrane anchoring sequence, into FPV. There is no teaching or suggestion in Yoshida of combining the gB signal sequence of MDV with a different antigenic gene than the sequence coding for the corresponding MDV protein.

Thus, even if, arguendo, a person of the art attempted to modify Sajto by referring to Yoshida, that person would not be motivated to replace the NDV sequence of Sajto by a MDV sequence as in Yoshida. Specifically, since Yoshida uses the signal, anchoring and coding sequences of the same gB gene, a person of ordinary skill in the art would find absolutely no guidance in Yoshida as to whether the MDV gB signal and membrane anchoring sequence could be successfully severed from the rest of the gB sequence and combined with a different antigen gene than gB to successfully produce a hybrid DNA and a corresponding fusion protein. As a result, the present claims are not obvious over any combination of Sajto and Yangida.

In addition, with respect to claims 29-30 and 41, it is submitted that these claims recite in vivo activity. Therefore, for this reason alone, these claims are not obvious over any combination of Sajto and Yoshida.

Further, with respect to claims 43-44 (claim 43 recites the absence of a membrane anchoring sequence and claim 44 recite secretion outside of the cell), it is submitted that both Sajto and Yoshida describe the production of an antigenic protein with both a signal sequence and a membrane anchoring sequence. Specifically, Sajto discloses combining NDV-HN signal peptide region including NDV-HN membrane anchoring peptide region in hybrid combination with Mg antigenic protein, and Yoshida dislcoses using the full MDVgB signal peptide region with MDVgB antigenic protein and MDVgb membrane anchoring region.

Thus, the fusion protein expressed in Sajto may be transferred to the vicinity of the cell membrane, because the hydrophobic peptide region such as the signal peptide and the membrane anchoring peptide has an affinity to the cell membrane which is composed of lipid bilayer and is highly hydrophobic. However, since the expressed fusion protein has the membrane anchoring region, the fusion protein of Sajto remains expressed on the surface of the cell, and is not released from the cell to be expressed outside the cell, which explains the disappointing immunization results in vivo.

Similarly, the protein expressed in Yoshida has the full length of gB and contains the signal sequence and the membrane anchoring sequence. Thus, the protein of Yoshida is transferred to the vicinity of a cell membrane, and the signal peptide and membrane anchoring peptide gain entrance into the cell membrane. However, the boundary between the membrane anchoring sequence and the antigenic protein is not cut off, so that the protein remains ligated with the membrane anchoring peptide and is not expressed outside the cell.

In contrast, in the present invention as recited in present claims 43-44, the membrane anchoring sequence is not ligated with the DNA sequence coding for the antigenic protein, and the

antigenic protein is expressed outside the cell, respectively. In other words, the present inventors have discovered that an essential problem in Sajto and Yoshida resides in that the antigenic protein is not secreted to the outside of the cell, and accordingly, they have provided for ligating only the signal sequence, not the membrane anchoring sequence, to the antigenic gene, so that the antigenic protein can be secreted to the outside fo the cell while efficiently transferring the antigenic protein to the cell membrane, thereby attaining satisfactory immunization effects in vivo. This feature of the present invention and its advantages are not disclosed in any of Sajto and Yoshida, and therefore, present claims 43-44 are not obvious over any combination of Sajto and Yoshida.

In view of the above, it is submitted that the prior art rejections should be withdrawn.

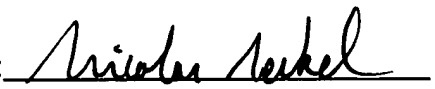
In conclusion, the invention as presently claimed is patentable. It is believed that the claims are in allowable condition and a notice to that effect is earnestly requested.

In the event there is, in the Examiner's opinion, any outstanding issue and such issue may be resolved by means of a telephone interview, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number listed below.

In the event this paper is not considered to be timely filed, the Applicants hereby petition for an appropriate extension of the response period. Please charge the fee for such extension and any other fees which may be required to our Deposit Account No. 01-2340.

Respectfully submitted,

ARMSTRONG, WESTERMAN & HATTORI, LLP

By: 

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Encls.: Exhibits A and B
Abstract of Eur. J. Biochem., 213, 3, 1333-1340 (1993)
Abstract of Cell Immunol., 69, 2, 226-237 (1996)